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Trimetazidine: a new concept in the treatment of angina Comparison with propranolol in patients with stable angina

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1 Trimetazidine has a direct anti-ischaemic effect on the myocardium without altering the rate × pressure product or coronary blood flow.
2 The effects of trimetazidine (20 mg three times daily) were compared with those of propranolol (40 mg three times daily) in a double-blind parallel group multicentre study in 149 men with stable angina.
3 Reproducibility of exercise performance was verified during a 3 week run-in placebo washout period. All patients had > 1 mm ST-depression on exercise test.
4 After 3 months, similar anti-anginal efficacy was observed between the trimetazidine (n = 71) and propranolol (n = 78) groups. No significant differences were observed between trimetazidine and propranolol as regards anginal attack rate per week (mean difference P − TMZ: −2; 95% CI: −4.4, 0.5) and exercise duration (mean difference P − TMZ: 0 s; 95% CI: −33, 34) or time to 1 mm ST segment depression (mean difference P − TMZ: 13 s; 95% CI: −24, 51). Heart rate and rate × pressure product at rest and at peak exercise remained unchanged in the trimetazidine group but significantly decreased with propranolol ($P < 0.001$ in all cases). With both drugs there was a trend to decreased ischaemic episodes in the 46% patients who experienced ambulatory ischaemia on Holter monitoring. Six patients stopped trimetazidine and 12 propranolol. Of these, five in each group were withdrawn because of deterioration in cardiovascular status.
5 The results suggest that trimetazidine and propranolol at the doses studied have similar efficacy in patients with stable angina pectoris. The unchanged rate × pressure product suggests that the mechanism of action of trimetazidine is not primarily reduction in energy demand.

Keywords trimetazidine propranolol angina pectoris exercise testing Holter monitoring

Introduction

Trimetazidine is a 1-(2,3,4 trimethoxybenzyl) piperazine dihydrochloride salt ($C_{14}H_{22}O_3N_2$,2HCl) which displays anti-ischaemic effects without inducing any significant haemodynamic changes [1]. Its anti-anginal efficacy has been documented in controlled studies against placebo [2–5] and nifedipine [6]. An unchanged rate × pressure product at rest and at peak exercise in humans [3, 4, 6], and unchanged coronary blood flow in dogs [7] suggest that trimetazidine may exert its anti-ischaemic effect at the cellular level. In patients undergoing coronary angioplasty, intracoronary administration of trimetazidine delays the development and reduces the magnitude of the ischaemic response without modifying systemic haemodynamics [8, 9]. Beneficial effects have also been reported in ischaemic cardiomyopathy [10] and during coronary artery bypass surgery [11]. Brottier *et al.* [10] reported that trimetazidine significantly improved clinical status and isotopic ejection

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fraction, and decreased cardiac volume after 6 months treatment. In patients undergoing coronary artery bypass surgery, oral pre-treatment with trimetazidine and addition of trimetazidine to the cardioplegic solution decreased release of malondialdehyde and myosin in the coronary sinus after reflow. Trimetazidine has also been shown to preserve energy balance, prevent intracellular acidosis and reduce free-radical-induced injury in numerous experimental models of ischaemia (see review by Harpey *et al.* [12]). However, the precise mechanisms by which trimetazidine exerts its effects remain to be determined [1].

No data comparing trimetazidine with a β-adrenergic receptor blocking agent are available. The aim of this multicentre study was to compare trimetazidine with propranolol in patients with stable angina using a double-blind design and an intention-to-treat analysis.

Methods

Pharmacology and pharmacokinetics of trimetazidine

Trimetazidine is more than 95% non-ionised at physiological pH, permitting the drug to pass through lipoprotein membranes [13]. In man, it is rapidly and completely absorbed from the gastrointestinal tract. Plasma protein binding is low and the volume of distribution is 320 l. Four pathways of metabolism are known but metabolism is not extensive, with 51% of unchanged drug eliminated in urine. Elimination is rapid ($t_{1/2} \simeq 6$ h) and predominantly renal. No kinetic interaction is found with theophylline, digoxin or antipyrine and food intake does not modify trimetazidine [14].

Patients

The Trimetazidine European Multicenter Study was performed from June 1988 to March 1991 in 19 centres in 10 European countries. Men with stable exertional angina were included in this double-blind study. All patients had age < 70 years; stable exertional angina [15] for at least 1 month, with slight or marked limitation of everyday activity (Canadian Heart Association, grade II or III [16]); a positive exercise test defined as either typical anginal pain and 1 mm ST segment depression (1 mm = 0.1 mV) or more, with the ST segment extending horizontal or down-sloping for at least 80 ms after the J point, or ST segment depression ⩾ 3 mm without anginal pain; and a maximal workload level between 60 and 150 watts. The presence of coronary lesions was confirmed by coronary angiography showing stenosis of at least one major coronary artery or by a history of previous myocardial infarction. Patients were excluded if they had acute myocardial infarction within the previous 3 months, unstable angina, heart failure, uncontrolled hypertension, valvular disease, severe cardiac arrhythmia, second- or third-degree atrioventricular block, resting sinus bradycardia less than 50 beats min^{-1}, or Wolff-Parkinson-White Syndrome. Patients with asthma, peripheral vascular disease, or insulin-treated diabetes mellitus were excluded, as were patients currently treated with drugs that could interfere with anti-anginal treatment (β-adrenoceptor blockers or calcium antagonists prescribed as antihypertensive agents, amiodarone prescribed as antiarrhythmic agent), or drugs that could interfere with the interpretation of the ST segment changes (mainly antiarrhythmic drugs and digoxin). Patients who had been treated with either propranolol or trimetazidine as an anti-anginal drug were also excluded. The study was approved by Ethics Committees of each participating institution. Patients were informed about the possible risks and benefits of participating in the study and gave informed consent.

Study design

During the placebo run-in phase all anti-anginal medications were discontinued except sublingual nitroglycerin for the control of anginal attacks. Anginal attacks, nitroglycerin consumption and level of activity were recorded by diary. At the end of the first week (D^{-14}), the first exercise test and 24 h ambulatory ECG were performed. Patients who fulfilled the selection criteria received placebo during a 2 week period, then (D^0) a second exercise test and 24 h ambulatory ECG were performed. Patients included met the following criteria: 1) a minimum of 3 anginal attacks/week during the placebo period and 2) exercise duration reached at D^0 compared with D^{-14} did not show a variation of more than 2 min within the same work level or 1 min if the work level was different. During the double-blind phase patients received at random either propranolol 40 mg three times daily or trimetazidine 20 mg three times daily. Titration of study medication was allowed at D^{15} according to individual clinical efficacy and acceptability. If there were side effects the dose could be decreased by one tablet. Conversely, with insufficiently controlled angina pectoris, the dose could be increased by one tablet per day (i.e. to propranolol 160 mg day^{-1} or trimetazidine 80 mg day^{-1}). Thereafter dosage was not changed, and active therapy was for 3 months. Clinical examination, exercise tolerance test and 24 h ambulatory ECG monitoring were performed 30 (D^{30}) and 90 (D^{90}) days after randomization.

Clinical evaluation

An anginal diary was filled out by the patients throughout the study. The frequency of anginal attacks, nitroglycerin consumption and any symptoms were reviewed at each visit.

Exercise tolerance tests

For each patient exercise tests were symptom-limited maximal tests performed on the same electromechanically braked bicycle ergometer, by the same investigator and at the same time of day. Patients were evaluated in the morning, before lunch, 3 to 4 h after study medication intake, and more than 2 h after short-acting nitrates. Smoking was not allowed for 2 h preceding the test. The

initial workload of 30 watts was increased by 30 watts every 3 min. A 3-lead orthogonal (AVF, V2 and V5) electrocardiogram was continuously monitored. Blood pressure (BP), heart rate (HR) and electrocardiographic recordings (ECG) were obtained: i) at rest; ii) either every minute (HR, ECG) or every 3 min (BP) during exercise; iii) at peak exercise; and iv) every minute (HR, ECG) or every 3 min (BP) during recovery. During the active treatment phase, exercise was stopped on the appearance of at least one of the following criteria: typical anginal pain and ST segment depression $\geqslant$ 1 mm compared with baseline, with the ST segment horizontal or down-sloping for at least 80 ms after the J point; ST segment depression $\geqslant$ 3 mm; systolic BP $\geqslant$ 260 mm Hg; fatigue or dyspnoea; arrhythmias, frequent premature ventricular contractions—more than 10% of the complexes, polymorphous doublets, in runs, or R/T phenomenon; or acute left ventricular failure. The exercise test variables analyzed were exercise duration (s), total work performed at peak exercise (Kpm), ST segment depression at peak exercise (mm), time to 1 mm ST depression (s), heart rate, systolic blood pressure, rate × pressure product at peak exercise and at the level corresponding to the maximum exercise test at inclusion (D^0).

Ambulatory ECG monitoring

Ambulatory 24 h ECG tapes were analyzed according to a previously described protocol [17]. Briefly, the ST-segment modifications were computerized and analysed by means of a semi-automated algorithm in order to quantify myocardial ischaemia reliably. Ischaemic episodes were included for analysis when there was ST segment depression of 1 mm below baseline ST segment level for at least 1 min with the ST segment horizontal or down-sloping for at least 80 ms after J point. Data recorded were the number of ischaemic episodes, the total ischaemic time, the total ischaemic area, i.e. the integral of the ST segment (mm × min). Analysis included only those patients who had experienced at least one ischaemic episode during the study.

Evaluation

The effects of anti-anginal therapy were evaluated at D^{30} and D^{90} using primary and secondary evaluation criteria.

Primary criteria were: the severity of angina assessed as the number of anginal attacks and the ergometric parameters, especially effort duration and time to 1 mm ST segment depression. For patients who did not experience 1 mm ST depression during the treatment period the time to 1 mm ST depression was replaced by the exercise duration. Similarly time to angina was replaced by the exercise duration for patients who did not experience angina during the test. Complementary information was sought using secondary evaluation criteria: nitrate consumption and ambulatory 24 h ECG monitoring. Ambulatory 24 h ECG tapes were referred to a central bank and centralized analysis was performed. Tapes were interpreted by a physician unaware of medication assignment.

Statistical analysis

Comparability between groups for clinical characteristics of the study population was tested by a two tailed Student's *t*-test for independent samples for quantitative parameters and by a χ^2 test for qualitative parameters [18]. Stability over time and comparability between groups for exercise performance results were tested by a two way analysis of variance (Group × Time) with repeated measurements on time [19]. Stability was assessed by no significant Time effect, comparability by no significant Group effect.

According to the intent to treat analysis [20], analysis of efficacy involved all randomized patients and thus included those who deviated from the protocol and those whose treatment was stopped. When treatment was stopped before D^{90}, the last value on treatment was used for this end point analysis. Analysis of Holter monitoring data involved only patients who experienced transient ischaemic episodes during everyday activity.

To compare the difference between treatments in severity of anginal pain a Cochran Mantel Haenszel test with modified ridit scores and stratification on levels at D^0 was performed.

Other quantitative variables were analysed by a two way analysis of variance (Group × Time) with repeated measurements on time. Differences between groups were assessed by Groups × Time interaction and expressed in the text by the difference between treatments. Mean and 95% CI of this difference are presented in tables.

As a complementary analysis change over time within groups was tested by one way analysis of variance with repeated measurements (mean changes and 95% CI of these changes are presented in tables).

A two way analysis of variance was performed on fully documented patients and only described on exercise performance results.

Results

Study population

One hundred and forty-nine men (mean age 57 years) were entered. Their characteristics are shown in Table 1. One hundred and thirty-one patients completed the study, 125 (84%) in full accord with the protocol. Eighteen patients discontinued: 6 in the trimetazidine group, 12 in the propranolol group. On trimetazidine withdrawals were due to myocardial infarction (1), worsening of angina (4), or poor patient compliance (1). On propranolol withdrawals were due to myocardial infarction (1), worsening of angina (3), supraventricular tachycardia during exercise (1), bradycardia (2), cold extremities (1), gastrointestinal symptoms (1), malaise (1), deviation from the protocol (1) and moving abroad (1). No patient was lost to follow-up.

Initial dosages were maintained throughout the study in 60 and 59% of patients in the trimetazidine and propranolol groups respectively. Doses were lowered in 3 and 4% and were increased in 37 and 37% of the

patients of the timetazidine and propranolol groups respectively. The mean daily doses were 132 ± 3 mg (propranolol) and 67 ± 1 mg (trimetazidine).

Table 1 Clinical characteristics of the study population and coronary angiography results

	Trimetazidine (n = 71)	*Propranolol* (n = 78)
Age (years)	58 ± 1	57 ± 1
Weight (kg)	77 ± 1	78 ± 1
Duration of angina pectoris (months)	52 ± 7	46 ± 8
Previous antianginal treatment (%)		
None	20	19
Monotherapy	34	40
Combination therapy	46	41
Previous myocardial infarction, Yes (%)	54	51
Coronary angiography history, Yes (%)	69	74
Coronary artery stenosis, %		
1 vessel disease	31	35
2 vessel disease	47	41
3 vessel disease	22	24

Values are means and standard error of mean or percentage.

Clinical evaluation

At baseline (D^0) no significant differences between groups in clinical characteristics were revealed (Table 1). No significant differences were observed between trimetazidine and propranolol groups for improvement of angina status in patients with end-point data. Relative to baseline, both trimetazidine and propranolol treatments decreased the severity of anginal pain. Table 2a shows that 24/71 and 31/78 patients who had anginal pain during ordinary physical activity when they entered the trial became asymptomatic after trimetazidine and propranolol treatment respectively. This was associated with a decrease in grade II and grade III status within each group. The angina attack rate and nitrate consumption per week are shown for patients with end point data (Table 2b). No significant differences were observed between the two groups (mean difference P – TMZ: −2.0; 95% CI: −4.4, 0.5). In the 149 patients included in the trial, both trimetazidine and propranolol reduced the average number of anginal attacks per week ($P = 0.001$ and $P < 0.001$ respectively) and the mean consumption of nitroglycerin per week ($P = 0.036$ and $P < 0.001$ respectively) (Table 2b). Twenty-one patients (29.6%) in the trimetazidine group and 30 patients (38.5%) in the propranolol group reported complaints spontaneously during the study. Spontaneous complaints are listed in Table 3. Their intensity was mostly mild to moderate.

Table 2a Grades of exertional angina (from history) before and after anti-anginal therapy

Grades at D^0	*Treatment*	*Grades at END* I	II	III	IV	*Probability (*)*
II	Trimetazidine	23	31	2	0	$P = 0.176$
	Propranolol	28	27	4	0	
III	Trimetazidine	1	5	8	1	
	Propranolol	3	11	5	0	

(*) Difference between groups stratified by grades at D^0 and tested by a Cochran Mantel Haenszel test on modified ridit scores.

Table 2b Severity of anginal pain (from diary) before and after anti-anginal therapy

	Trimetazidine (n = 71) D^0	*End*	*Propranolol* (n = 78) D^0	*End*	*Difference of changes P – TMZ Mean 95% CI*	*Comparison of changes between groups*
Average number of attacks	10.1	6.6	9.4	3.9	−2.0 [−4.4, 0.5]	$P = 0.117$
Per week	−3.5 [−5.5, −1.5] $P = 0.001$		−5.5 [−7.0, −4.0] $P < 0.001$			
Consumption of nitroglycerin	8.6	6.2	6.6	3.2	−1.1 [−3.7, 1.6]	$P = 0.426$
Units per week	−2.4 [−4.6, −0.2] $P = 0.036$		−3.5 [−4.9, −2.0] $P < 0.001$			

Values are means and 95% confidence intervals.

Table 3 Incidence of spontaneous complaints

Symptom	*Trimetazidine group* (n = 71) n	%	*Propranolol group* (n = 78) n	%
Fatigue	5	7.0	4	5.1
Dizziness	5	7.0	3	3.9
Sleep disturbances	2	2.8	5	6.4
Muscular cramps	5	7.0	1	1.3
Cold extremities/Raynaud's phenomenon	1	1.4	5	6.4
Effort-induced discomfort	4	5.6	2	2.6
Gastralgia/oesophagitis	2	2.8	4	5.1
Dyspnoea	2	2.8	3	3.9
Headache	1	1.4	3	3.9
Cutaneous signs	1	1.4	3	3.9
Sexual disturbances	0	0.0	3	3.9
Paresthesiae	0	0.0	3	3.9
Nervousness	1	1.4	2	2.6
Depression	2	2.8	0	0.0
Orthostatic hypotension	0	0.0	2	2.6
Asthma/bronchospasm	1	1.4	0	0.0
Sedation/drowsiness	1	1.4	0	0.0
Palpitations	1	1.4	0	0.0
Visual disturbances	1	1.4	0	0.0
Constipation	1	1.4	0	0.0
Diarrhoea	0	0.0	1	1.3
Nausea	0	0.0	1	1.3

Exercise tolerance tests

Reproducibility of exercise performance was confirmed by comparing the results of tests at the beginning (D^{-14}) and end (D^0) of the run-in phase. Patients in the propranolol group were less stable for exercise duration, but we consider that this difference is not clinically significant because a variation of up to 2 min was allowed in the protocol. No significant differences between the groups were observed as regards time to 1 mm ST depression, maximum ST depression, and rate × pressure product at peak exercise (Table 4).

Patients with end point data Analysis of variance showed no significant differences between propranolol and trimetazidine as regards exercise duration (mean difference P − TMZ: 0 s; 95% CI: −33, 34), time to 1 mm ST segment depression (mean: 13 s; 95% CI: −24, 51) and maximum ST segment depression and/or time to angina (Table 5). Both trimetazidine and propranolol significantly increased exercise duration ($P = 0.010$ and $P = 0.005$, respectively), time without ischaemia (both $P < 0.001$), time to angina ($P < 0.001$), and significantly decreased maximum ST segment depression ($P = 0.021$ and $P < 0.001$, respectively) (Table 5). After treatment, 23/71 patients (32.4%) in the trimetazidine group and 19/78 patients (24.4%) in the propranolol group no longer experienced ST depression ⩾ 1 mm during exercise (P = NS).

Changes in resting heart rate and rate × pressure product differed significantly between the propranolol and trimetazidine groups ($P < 0.001$). Compared with baseline values, propranolol therapy significantly decreased resting heart rate ($P < 0.001$), systolic pressure ($P = 0.012$) and rate × pressure product ($P < 0.001$). Heart rate, systolic pressure and rate × pressure product at rest remained unchanged on trimetazidine therapy. Analysis of variance showed significant differences between propranolol and trimetazidine for haemodynamic parameters at peak exercise ($P < 0.001$). Compared with D^0 values, heart rate at peak exercise significantly decreased with propranolol (from 131 ± 2 to 111 ± 2 beats min^{-1}, $P = 0.001$) whereas it increased slightly with trimetazidine (from 126 ± 2 to 129 ± 2 beats min^{-1}, $P = 0.018$). Similarly, the rate × pressure product at peak exercise decreased significantly on propranolol (from 23 683 ± 565 to 18 579 ± 547 mm Hg × beats min^{-1}, $P < 0.001$) whereas it did not alter on trimetazidine (from 22 387 ± to 23 089 ± 647 mm Hg × beats min^{-1}, P = NS).

Patients with complete data Figure 1 shows the changes in exercise tolerance tests for patients who completed the study in full accordance with the protocol. No significant differences were observed between groups for effort duration, time to 1 mm ST segment depression, time to angina and in maximum ST segment depression. The rate × pressure product remained unchanged on trimetazidine whereas it decreased significantly on propranolol, both at rest and at peak exercise (between groups $P < 0.001$ both at rest and at peak exercise). Both groups showed a significant increase in

Table 4 Exercise performance: results during the run-in phase. Values are means and standard errors

		Trimetazidine (n = 71) D^{-14}	D^0	*Propranolol* (n = 78) D^{-14}	D^0	*Group effect* (*)	*Time effect* (*)
Exercise (s)	Mean	533	536	531	554	$P_{D0} = 0.515$ (**)	
	s.d.	179	171	181	171		
Time to 1 mm STD (s)	Mean	417	432	421	446	$P = 0.747$	$P = 0.002$
	s.d.	176	176	178	173		
Max ST depression (mm)	Mean	1.8	1.7	2.0	1.8	$P = 0.208$	$P = 0.011$
	s.d.	0.7	0.7	1.0	1.0		
RPP at peak exercise (mm Hg) × beats min^{-1}	Mean	22 466	22 387	23 967	23 683	$P = 0.075$	$P = 0.464$
	s.d.	4844	5499	4561	4959		

RPP = Rate pressure product; STD: ST segment depression;
(*) Group effect and Time effect in case of none significant interaction (Group × Time).
(**) P_{D0} = Comparability at D^0 because of a significant interaction (Group × Time).

Table 5 Exercise test results before and after anti-anginal therapy

	Trimetazidine (n = 71) D^0	*End*	*Propranolol* (n = 78) D^0	*End*	*Difference of changes Propranolol – TMZ Mean 95% CI*	*Comparison of changes between groups*
Exercise duration (s)	536	569	554	588	0 [−33, 34]	$P = 0.982$
	33 [8, 58] $P = 0.010$		33 [10, 57] $P = 0.005$			
Time to 1 mm STD (s)	432	483	446	510	13 [−24, 51]	$P = 0.481$
	50 [22, 79] $P < 0.001$		64 [37, 90] $P < 0.001$			
Maximum STD (mm)	1.72	1.46	1.79	1.41	−0.13 [−0.41, 0.16]	$P = 0.385$
	−0.26 [−0.47, −0.04] $P = 0.021$		−0.38 [−0.57, −0.19] $P < 0.001$			
Time to angina (s)	430	497	447	4,002	−4 [−40, 32]	$P = 0.830$
	67 [43, 92] $P < 0.001$		64 [−39, 89] $P < 0.001$			
Total work (kpm)	3,472	3,802	3,674	511	−2 [−382, 379]	$P = 0.993$
	330 [39, 621] $P = 0.027$		328 [76, 581] $P = 0.011$			

Values are means and 95% confidence interval.
STD: ST segment depression. In cases where 1 mm ST segment depression and/or angina were not experienced, time to 1 mm STD and time to angina were replaced by the exercise duration value.

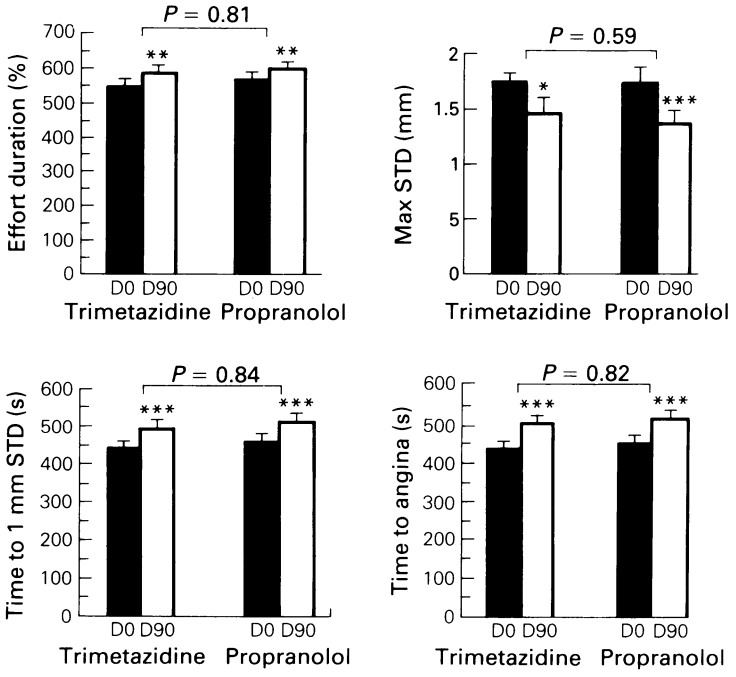

Figure 1 Exercise test results: evolution after 3 months of treatment in the patients who completed the study according to the protocol in the trimetazidine ($n = 62$) and the propranolol ($n = 63$) groups. STD = ST segment depression. Exercise duration was considered as a censored value for time to 1 mm STD and for time to angina when patients did not experience a 1 mm STD or anginal pain during effort. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

Table 6 Holter monitoring results: outcome in the trimetazidine (n = 36) and in the propranolol (n = 32) groups

	Trimetazidine (n = *36*) D^0 *End*	*Propranolol* (n = *32*) D^0 *End*	*Difference of changes* P – TMZ Mean 95% CI	*Comparison of changes between groups*
Number of ischaemic episodes	2.03 1.75 −0.28 [−1.03, 0.47] P = 0.456	2.69 2.56 −0.12 [−1.35, 1.10] P = 0.836	0.15 [−1.22, 1.53]	P = 0.825
Total ischaemic time (min)	37 29 −8 [−21, 5] P = 0.217	38 51 13 [−19, 45] P = 0.420	21 [−12, 53]	P = 0.203
Total ischaemic area (mm min)	−34 −27 8 [−6, 22] P = 0.263	−35 −49 −14 [−42, 13] P = 0.301	−22 [−52, 7]	P = 0.138

Values are means and 95% confidence interval.

effort duration, time to 1 mm ST segment depression, time to angina and a significant decrease in maximum ST segment depression (Figure 1).

Holter monitoring Ambulatory ECG monitoring showed that 68/149 patients (46%) had transient ischaemic episodes during everyday activity throughout the trial. At inclusion, one hundred and sixty-five transient ischaemic episodes were recorded, most of which (64%) were silent. Changes in the mean number of ischaemic episodes did not differ significantly between the two groups (P = 0.825) (Table 6). The number decreased, although not significantly, in both trimetazidine (from 2.03 ± 0.36 to 1.75 ± 0.33, n = 36) and propranolol groups (from 2.69 ± 0.38 to 2.56 ± 0.61, n = 32). The total ischaemic time did not differ between the two groups (P = 0.203). The total ischaemic time was not significantly modified in the trimetazidine group (from 37 ± 7 to 29 ± 6 min, n = 36) or in the propranolol group (from 38 ± 7 to 51 ± 19 min, n = 32). The total ischaemic area did not differ between the two groups (P = 0.138). The total ischaemic area decreased not significantly in the trimetazidine group (from −34 ± 7 to −27 ± 6 mm.min) and was not significantly modified in the propranolol group (from −35 ± 10 to −49 ± 19 mm min). Figure 2 illustrates individual variations of total ischaemic time in both groups.

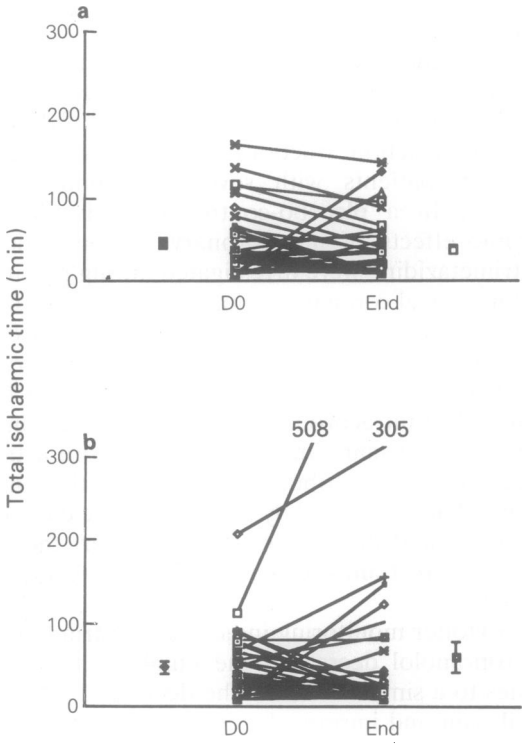

Figure 2 Individual variations of the total ischaemic time in a) the trimetazidine (n = 36) and b) in the propranolol group (n = 32). The two cases with erratic behaviour in the propranolol group are worth noting.

Discussion

Our study confirms the antianginal efficacy of trimetazidine previously documented in smaller controlled studies *vs* either placebo [2–5], or nifedipine [6].

Trimetazidine and propranolol produced similar increases in exercise duration and ischaemic threshold, and decreases in maximum ST-segment depression. Propranolol significantly decreased heart rate and systolic pressure both at rest and at peak exercise, and this resulted in a significantly lower double product. The rate × pressure product has been considered an index of myocardial oxygen consumption during exercise in patients with angina pectoris [21]. These effects of propranolol are consistent with improved exercise tolerance mediated by the reduction in cardiac work and myocardial oxygen demand both at rest and during exercise. Conversely, neither heart rate nor systolic pressure were modified by trimetazidine at rest, and improved exercise tolerance was associated with an unchanged rate × pressure product at peak exercise.

This suggests that the improved exercise tolerance is not associated with a decrease in myocardial oxygen demand. Three main mechanisms could explain the anti-anginal efficacy of trimetazidine: increased coronary blood flow, decreased myocardial contractility, or a direct anti-ischaemic effect at the cellular level [22].

Trimetazidine does not modify coronary blood flow in dogs [7]. A negative inotropic effect has not been observed in experimental [23] and clinical [24] studies. This study is consistent with much experimental work documenting an anti-ischaemic effect of trimetazidine directly at the cellular level. Trimetazidine demonstrated cytoprotection in guinea-pig isolated left ventricle during ischaemia [25]. Using nuclear magnetic resonance spectroscopy, trimetazidine significantly reduced acidosis and inorganic phosphate accumulation during ischaemia, and increased creatine rephosphorylation during reperfusion in the rat isolated heart [26]. Limitation of both intracellular acidosis and accumulation of sodium and calcium have also been reported [27]. Cellular protection from free radical damage during ischaemia [28, 29] and prevention of energy metabolism imbalance [30] may also be involved in the cardioprotective effect.

Two clinical studies have reinforced these experimental results. In a placebo-controlled study Brottier *et al.* [10] reported that trimetazidine improved clinical status and ejection fraction, and decreased cardiac volume in patients with severe ischaemic cardiomyopathy. In a placebo-controlled study the anti-ischaemic effects of intracoronary administration of 6 mg trimetazidine were investigated during percutaneous transluminal coronary angioplasty [9]. Trimetazidine significantly delayed the development and reduced the magnitude of the ischaemic response on intracoronary ECG, without modifying heart rate or arterial blood pressure. The intracoronary ECG was derived directly via the intra-coronary angioplasty guide wire acting as an electrode so as to obtain an ECG directly from the myocardial area supplied by the vessel to be dilated [9]. These data, and the present study, support the hypothesis of a direct anti-ischaemic effect of trimetazidine in humans.

ECG Holter monitoring indicated that trimetazidine and propranolol decreased the number of ischaemic episodes to a similar extent. The decreased severity of anginal pain and improved exercise performance contrasted with the lack of improvement in total ischaemic area under both trimetazidine and propranolol. However, previous studies have clearly shown that therapies directed toward symptom control may be insufficient fully to control silent ischaemia [31]. Furthermore, our Holter monitoring data have to be interpreted with caution since ambulatory ischaemia was not a criterion for selection and the sample size in each group was small. The lack of efficacy of propranolol on ambulatory ischaemia is likely explained by two cases with extreme results (Figure 2).

Our results indicate that trimetazidine was as efficient as 120 to 160 mg propranolol in patients with stable angina pectoris. It has been previously shown that 160 mg propranolol is adequate for treating such patients [32]. Although the mean dose of propranolol used in our study was slightly below this value, the decreased heart rate at peak exercise confirmed β-adrenoceptor blockade in the propranolol group. Furthermore, Furberg *et al.* [33] reported that a majority of patients with stable angina pectoris responded to a dose of 120 mg or less, and that 112 mg was the mean optimal dose. Thus, the 132 mg mean daily dose of propranolol used in the present study is within the range of 112–160 mg previously recommended [32, 33].

The results of studies *vs* active comparator must be interpreted carefully because the lack of statistically significant difference is not synonymous with similarity. There was no placebo in this study and it has been demonstrated that placebo can improve both the symptoms and exercise performance in patients with angina. It is important to note that it has been demonstrated that trimetazidine had greater antianginal efficacy than placebo [2–5], and that is one reason why this study was not placebo-controlled. A second reason was difficulty from an ethical point of view in giving placebo for nearly 4 months to patients suffering from grade II–III coronary artery disease.

In conclusion, this study suggests similar efficacy of trimetazidine and propranolol in patients with stable angina pectoris. The lack of rate × pressure product modification with trimetazidine suggests that trimetazidine does not primarily reduce energy demand. Anti-ischaemic drugs without haemodynamic effects may be useful [1], and trimetazidine deserves further evaluation.

Appendix

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